NOTE TO APPLICANTS: IT IS IMPORTANT FOR YOU TO INCLUDE ALL RELEVANT INFORMATION ABOUT YOUR RESEARCH IN THIS APPLICATION FORM AS YOUR ETHICAL APPROVAL WILL BE BASED ON THIS FORM. THEREFORE ANYTHING NOT INCLUDED WILL NOT BE PART OF ANY ETHICAL APPROVAL.

YOU SHOULD READ THE ETHICS APPLICATION GUIDELINES AND HAVE THEM AVAILABLE AS YOU COMPLETE THIS FORM.

APPLICATION FORM

SECTION A APPLICATION FOR ETHICAL REVIEW: HIGH RISK

A1

Project Title: Utility of in vivo skin blister models to detect inflammatory modulation by pharmacological agents

Date of Submission: 30/Jan/2023	Proposed Data Collection Start Date: 01/Mar/2023
UCL Ethics Project ID Number: 23833/002	Proposed Data Collection End Date: 01/Oct/2023

Is this application for continuation of a research project that already has ethical approval? ***For example, a preliminary/pilot study has been completed and this is an application for a follow-up project? If yes, please provide the information requested below.***

Project ID for the previous study: 5060_003

A2

Principal Researcher

Please note that a student – undergraduate, postgraduate or research postgraduate cannot be the Principal Researcher for Ethics purposes.

Full Name: Dr James Fullerton	Position Held: Honorary Clinical Lecturer, UCL; Associate Professor of Clinical Therapeutics, University of Oxford
Name and Address of Department: Centre for Precision Healthcare, Division of Medicine, UCL Rayne Building, 5 University Street, London, WC1E 6JF; Centre for Clinical Therapeutics, NDORMS, University of Oxford, Botnar Research Centre, Windmill Road, Oxford, OX3 7LD	Email: james.fullerton@ndorms.ox.ac.uk Telephone: 07803 729439 Fax: N/A

Declaration To be Signed by the Principal Researcher

- I have met with and advised the student on the ethical aspects of this project design *(applicable only if the Principal Researcher is not also the Applicant)*.
- I understand that it is a UCL requirement for both students & staff researchers to undergo Disclosure and Barring Service (DBS) Checks when working in controlled or regulated activity with children, young people or vulnerable adults. The required DBS Check Disclosure Number(s) is: N/A
- I have obtained approval from the UCL Data Protection Officer stating that the research project is compliant with the General Data Protection Regulation 2018. My Data Protection Registration Number is: **Z6364106/2022/10/05**
- I am satisfied that the research complies with current professional, departmental and university guidelines including UCL's Risk Assessment Procedures and insurance arrangements.
- I undertake to complete and submit the 'Continuing Review Approval Form' on an annual basis to the UCL Research Ethics Committee.
- I will ensure that changes in approved research protocols are reported promptly and are not initiated without approval by the UCL Research Ethics Committee, except when necessary to eliminate apparent immediate

hazards to the participant.

- I will ensure that all adverse or unforeseen problems arising from the research project are reported in a timely fashion to the UCL Research Ethics Committee.
- I will undertake to provide notification when the study is complete and if it fails to start or is abandoned.

SIGNATURE  **DATE:** 30/Jan/2023

A3 **Applicant(s) Details** *(if Applicant is not the Principal Researcher e.g. student details):*

Full Name: João Joaquim Dias de Matos Oliveira

Position Held *i.e.undergraduate/bachelor or masters project (if so, provide course title/number, PhD, staff led research project which may involve one or more students*: PhD student

Name and Address of Department: Centre for Precision Healthcare, Division of Medicine, UCL Rayne Building, 5 University Street, London, WC1E 6JF	Email: joao.oliveira.18@ucl.ac.uk Telephone: 07952 089135 Fax: N/A

Full Name: Prof Richard Day

Position Held: Associate Professor of Clinical Therapeutics, Professor of Regenerative Medicine

Name and Address of Department: Centre for Precision Healthcare, Division of Medicine, UCL Rayne Building, 5 University Street, London, WC1E 6JF	Email: r.m.day@ucl.ac.uk Telephone: +44 20 3108 52183 Fax: N/A

A4 **Sponsor/ Other Organisations Involved and Funding**

a) Sponsor: ☒ **UCL** ☐ **Other institution**
If your project is sponsored by an institution other than UCL please provide details: N/A

b) Other Organisations: If your study involves another organisation, please provide details. *Evidence that the relevant authority has given permission should be attached or confirmation provided that this will be available upon request.* N/A

c) Funding: What are the sources of funding for this study and will the study result in financial payment or payment in kind to the department or College? *If study is funded solely by UCL this should be stated, the section should not be left blank.* Funding is provided by a GSK-Academic Studentship. This supports investigator-led research at Higher Educational Institutes.

A5 **Signature of Head of Department [or Chair of your Departmental Research Ethics Committee/Departmental Ethics Lead]**
(This must not be the same signature as the Principal Researcher)

A. I have discussed this project with the principal researcher who is suitably qualified to carry out this research and I approve it.

I am satisfied that *[please highlight as appropriate]:*

(1) Data Protection registration:

- **has been satisfactorily completed**
- **has been initiated**
- **is not required**

(2) a risk assessment:

- **has been satisfactorily completed**
- **has been initiated**

(3) appropriate insurance arrangements are in place and appropriate sponsorship [funding] has been approved and is in place to complete the study. ☒ **Yes** ☐ **No**

(4) a Disclosure and Barring Service check(s):

- **has been satisfactorily completed**
- **has been initiated**
- **is not required**

Links to details of UCL's policies on the above can be found at: http://ethics.grad.ucl.ac.uk/procedures.php

****If any of the above checks are not required please clarify why below.**

PRINT NAME: Prof Derek Gilroy

SIGNATURE: [redacted] **DATE:** 30/Jan/2023

SECTION B DETAILS OF THE PROJECT

****It is essential that Sections B1 and B2 are completed in simple understandable lay language that a non-expert could understand or you risk your project being rejected**

B1 **Please provide a brief summary of the project in simple lay person's prose outlining the intended value of the project, giving necessary scientific background.** *(max 500 words).*

Inflammation is an evolutionarily conserved response to both external stimuli (e.g. bacteria) or to internal warning signals generated, for example, by damage to cells. Designed to protect the host organism, if unchecked or unbalanced, inflammation can also contribute to disease. It is thus vital that we understand how it is regulated so that we can control it therapeutically for patient benefit.
Controlled models in healthy human volunteers, where local inflammation is induced in a safe, consistent way, are useful tools to understand the biological process that determine the magnitude and duration of the inflammatory response. They also allow the assessment of the effect of drugs to be tested. The skin, as an easily accessible site, has commonly been employed for this purpose and the most widely used method to cause skin inflammation is blistering, induced by either negative pressure (suction) or a chemical (cantharidin). Both result in a localised inflammatory response and a blister that can easily be punctured to collect the fluid for analysis.
Whilst both means of producing a blister have been widely employed (including at UCL e.g. 5061/001,

2907/002, 5060/003) and are well tolerated, their comparability and relative value in different contexts is unknown. On a prior application (5060/003), we identified differences in cell numbers, their type and functional status in blisters, created by the two approaches, and taken at 24 hours post application of negative pressure or cantharidin. The implications of these findings is unclear, especially in the context of drug development.
This study aims to explore this comparison further, completing project 5060/003 (unable to continue due to Covid-19), and comparing the effect of known anti-inflammatory drugs (steroids) after both topical and systemic administration on blister and whole blood biomarkers. Importantly t will assess the ability and sensitivity of the two approaches to detect pharmacological manipulation of the immune system, via two different routes and at two timepoints (24 and 48hrs), within the same participant.
It is anticipated that comparison and characterisation of these models will inform the design of future experimental medicine and early phase drug discovery studies, allowing selection of the optimal approach to inflammation induction to answer specific scientific questions.

B2 **Briefly characterise in simple lay person's prose the research protocol, type of procedure and/or research methodology (e.g. observational, survey research, experimental). Give details of any samples or measurements to be taken** *(max 500 words).*

Non-smoking, healthy male volunteers aged 18 to 50 years will be recruited. Participants will be excluded if they have any medical problems or take regular medication (prescription or over-the-counter). Patients with tattoos, damaged skin or existing scars at the blistering site or with darker skin tone (Fitzpatrick scale V-VI) will also be excluded; the latter due to a higher risk of lasting skin discoloration following blistering. In line with other work in this field, only males have been selected to reduce variability in observed responses permitting a smaller number of participants overall.

In total, 6 volunteers will have blisters formed by the two different approaches, chemical and negative pressure, in three situations: control (moisturiser), following topical steroid and following systemic (oral) steroid exposure to enable comparison. This will occur over two part, each requiring three visits.

In the first part, participants will apply a known anti-inflammatory treatment (Betamethasone 0.1% Cream ~~hydrocortisone butyrate 0.1%~~ - a moderately potent steroid) and control agent (moisturiser - white soft paraffin) to one forearm each prior (3hrs) to blister induction. Blisters will be induced on the volar (hairless) surface of each forearm where the creams have been applied; one suction (for 24h collection) and two cantharidin blisters (for 24h and 48h collection) on each arm (6 blisters in total/participant). Suction blisters will be created using negative pressure equipment (NP-4, Electronic Diversities, USA) via a validated step-wise protocol. Chemical blisters will be raised using cantharidin (Cantharone - Dormer Laboratories, Inc.), an extract from blister beetles, using an established technique (as per previous applications). Blisters will be allowed to develop overnight, and will be protected by a dressing. On the second (24h post-blister induction - suction and cantharidin) and third days (48h - cantharidin only), blisters will be punctured with a sterile needle and their contents collected for analysis. Up to 5 blood samples (~10 mL each) per part of the study will also be collected to assess the systemic effect of the intervention at different times.

After a period of at least 14 days, subjects will return for part 2. Here they will be given prednisolone (30 mg, an orally active steroid), to be taken on the morning of the blistering procedure (3hrs prior). The same blistering procedure will be followed, however only one suction (24h) and 2 cantharidin blisters (for 24h and 48h collection) will be formed. Blood will again be taken prior to blister collection

On each blister collection day, after assessing blister volume and cellularity, blister and blood cells will be examined by flow cytometry to characterise their subtype and activation status. The blister supernatant will be cryopreserved alongside plasma to allow measuring of inflammatory mediators and detect the presence of study drugs. Blood samples will be incubated with a bacterial protein to observe the extent of stimulation, expected to be reduced by the drug.

At the end of the study, volunteers will be asked to record the healing of the blisters by taking photographs at regular intervals. Also, a questionnaire will be provided for participant feedback on each of the methods.

Attach any questionnaires, psychological tests, etc. (a standardised questionnaire does not need to be attached, but please provide the name and details of the questionnaire together with a published reference to its prior usage).

B3 **Where will the study take place (please provide name of institution/department)?**
If the study is to be carried out overseas, what steps have been taken to secure research and ethical permission in the study country? Is the research compliant with Data Protection legislation in the country concerned or is it compliant with the General Data Protection Regulation 2018?

Division of Medicine, UCL

B4 **Have collaborating departments whose resources will be needed been informed and agreed to participate?**
Attach any relevant correspondence.

N/A

B5 **How will the results be disseminated, including communication of results with research participants?**

The results will be published in peer-reviewed medical/scientific journals and/or presented at scientific conferences. Participants will have the option to have the finalised manuscript sent to them by email.

B6 **Please outline any ethical issues that might arise from the proposed study and how they are be addressed.** *Please note that all research projects have some ethical considerations so do not leave this section blank.*

a) Reimbursement. Participants will be recruited by email (using generic UCL mailing lists), local advertising through posters and word-of-mouth. Payment has been set at £200/subject to offer adequate compensation for time in the unit (estimated to total ~12 hours including travel), inconvenience and the interventional nature of the study (~£15/hr).

b) Cosmetic. The volunteers may develop a hyper or hypopigmented area on the forearm at the site of blister induction. It is expected that for subjects with darker skin pigmentation, a transient discoloration could persist for a longer period of time and be more noticeable. Given this risk, volunteers with Fitzpatrick scale V-VI skin will be excluded. Previous studies have demonstrated that altered pigmentation normally resolves within 4-6 weeks, however may take several months to fully return to normal. In our experience scarring does not occur but this risk will be stated explicitly. These aspects have been clearly identified in the participant information leaflet, and all participants will be verbally informed of this well in advance of the study.

c) Infection risk. Venupuncture and blister induction carry a small risk of infection (as the skin is broken). Venupuncture may additionally cause mild discomfort. All procedures will be carried out using aseptic non-touch technique where possible by experienced practitioners, trained in their performance. Participants will be followed up to ensure adequate healing. If any complications are suspected they will be referred to their GP or acute medical services as appropriate.

d) Cantharidin exposure. Cantharone is a drug containing cantharidin, manufactured to GMP standards by Dormer Laboratories Inc. It is a recognised medical treatment that is licensed for the treatment of warts in several countries. It has been safely and extensively employed for induction of inflammation-associated skin blisters for over 20 years at UCL and elsewhere. Side effects are considered extremely rare.

e) Steroid exposure. Betamethasone 0.1% Cream ~~Hydrocortisone butyrate 0.1%~~ cream is a topical anti-inflammatory medication that will be sourced from UCLH Pharmacy. The proposed study involves one single dose, applied onto healthy skin, which should have limited systemic effect and transient local immunomodulatory effect. Prednisolone (30 g) is an oral corticosteroid, which will be acquired from UCLH Pharmacy. This is a commonly used medication employed to treat allergy, inflammatory conditions, autoimmune disorders and cancers. Normal doses range from 5 to 80mg (depending on indication) and the selected dose is one that would be employed in acute exacerbations of airway disease. Prior studies exploring the pharmacology of prednisolone indicate it will induce a transient immunosuppressisve effect lasting up to 24 hours. Given as a single dose it is not anticipated to place individuals at risk of infection nor to suppress endogenous glucocorticoid production. There is a residual risk of sleep disturbance (minimised by morning dosing) and specific exclusion criteria (e.g. history of severe affective disroders / steroid-

induced psychosis, peptic ulcer disease etc.) and the recruitment of young healthy volunteers will minimise the risk of adverse events.

f) Data protection. All data will be pseudo-anonymised and linkable only via a master document to which the study team has access. Individuals will not be able to be identified via the forearm photos they are asked to submit.

SECTION C DETAILS OF PARTICIPANTS

C1 **Participants to be studied**

C1a. Number of volunteers:	6 subjects completing study (max 10 enrolled)
Upper age limit:	50
Lower age limit:	18

C1b. Please justify the age range and sample size:

This is an exploratory experimental medicine study employing multiple humoral and cellular endpoints. As such a formal power calculation has not been conducted. Literature review indicates that both topical and oral steroids should elicit a profound effect on the inflammatory response. As such, we estimate that 6 subjects and a within-subject design will provide sufficient data to reliably detect differences in the inflammatory response between exposure (control vs topical steroid vs oral steroid) and blister methodology (negative pressure vs chemical). This is supported by precedent in the field.

Data will be analysed after 3 subjects complete the study. If drug effect is not apparent, or dosing completely prevents blister formation, potency of steroid or dosage schedule will be evaluated. A protocol amendment will be submitted in this case to allow for change of dose and further 6 subjects will be evaluated with the new treatment regime.

To account for the possibility of a) drop-out b) volunteer acute illness c) inadvertent blister damage and d) treatment non-compliance, we may require recruitment of up to 4 additional volunteers to obtain the full number of volunteers to complete the study.

The age range has been selected to reduce heterogeneity (expected with older individuals) and minimise the risk of side effects from study drug exposure.

C2 **Accessing/Using Pre-Collected Data:**
If you are using data or information held by a third party, please explain how you will obtain this. You should confirm that the information has been obtained in accordance with the General Data Protection Regulation 2018.

N/A

C3 **Will the research include children or vulnerable adults such as individuals with a learning disability or cognitive impairment or individuals in a dependent or unequal relationship?** ☐ **Yes** ☒ **No**

How will you ensure that participants in these groups are competent to give consent to take part in this study? *If you have relevant correspondence, please attach it.*

N/A

C4

Will payment or any other incentive, such as gift service or free services, be made to any research participant?

☒ **Yes** ☐ **No**

If yes, please specify the level of payment to be made and/or the source of the funds/gift/free service to be used.

Payment will be £200 for completion of the study. If participant decides to withdraw before study completion, he will be entitled to a fraction of this amount, commensurate with the time already committed (e.g. completion of Part 1 only would provide £50 compensation).

Please justify the payment/other incentive you intend to offer.

Payment will compensate the subject's time and travel expenses taken for participating in the study plus the mild discomfort and transient cosmetic changes caused by the procedure. We estimate that the first visit to obtain consent will take approximately 1 hour, a visit to generate blisters should take approximately 4 hours and a visit to harvest the blisters and collect blood to take another hour. In total the subjects will be present in the unit for approximately 12 hours. Subjects will also be asked to comply with a strict regime of drug application and, in the end of the study, to complete a questionnaire on study experience and provide photographs of blister healing, taking additional time.

C5

Recruitment

(i) Describe how potential participants will be identified:

Self-identification and word-of-mouth. Posters will be placed around UCL, an advertising email will be sent to UCL students and staff via generic lists describing the study and potentially eligible individuals working in the Division of Medicine will be directly approached.

(ii) Describe how potential participants will be approached:

Contact details of study investigators are included on the advertising poster and email. Interested participants will be encouraged to email the PI and Applicant. Once contact is made, the PIS will be provided and eligibility discussed, prior to arranging a ~~ascertained the PIS will be provided and a~~ formal meeting ~~arranged~~.

(iii) Describe how participants will be recruited:

Participants will be asked to read the PIS and consider whether they want to take part in the study. At a subsequent meeting the study will be explained in detail to include design, timelines, potential side effects, commitments, expenses and the right not to participate and to withdraw at any time without penalty. If they are happy to proceed, an informed consent form will be signed and an appointment made to commence the study interventions.

C6

Will the participants participate on a fully voluntary basis? ☒ **Yes** ☐ **No**

Will UCL students be involved as participants in the research project? ☒ **Yes** ☐ **No**

If yes, care must be taken to ensure that they are recruited in such a way that they do not feel any obligation to a teacher or member of staff to participate.

Please state how you will bring to the attention of the participants their right to withdraw from the study without penalty?

The right to withdraw will be emphasised verbally during the consenting process as well as in the PIS. Awareness of this right will be indicated on the consent form.

C7

CONSENT

Please describe the process you will use when seeking and obtaining consent.

After confirmation of eligibility, potential volunteers will be provided with a copy of the PIS in advance (>24hrs) of a formal meeting where the study will be explained and - if they are happy to proceed - consent taken. This will allow time to read the details of the study, formulate questions and seek external advice if needed. At the meeting, all details of the study will be discussed including procedures, timelines, required visits to UCL as well as the potential side effects of participation. It will be highlighted that volunteers are under no obligation to participate and that they can withdraw at any time without penalty. Potential participants will be encouraged to ask the Investigators any questions. If they are willing to participate they will be asked to sign a consent form. If they want more time to consider participation this will be provided along with the opportunity to seek further clarification/more information.

A copy of your participant information sheet(s) and consent form(s) must be attached to this application. For your convenience proformas are provided in Appendix I. These should be filled in and modified as necessary.

In cases where it is not proposed to obtain the participants informed consent, please explain why below.

N/A

C8

Will any form of deception be used that raises ethical issues? If so, please explain.

No. This is an open label study

C9

Will you provide a full debriefing at the end of the data collection phase? ☐ **Yes** ☒ **No**

If 'No', please explain why below.

The outputs for this study will relate to group-level data on each model rather than individual responses. These data are not likely to be of interest to the volunteers taking part on the study as they have no direct clinical or health relevance. All data is expected to be disseminated in the scientific literature and participants will be offered the chance to receive a copy of these manuscripts.

C10

Information Sheets And Consent Forms: Appendix I

A poorly written Information Sheet(s) and Consent Form(s) that lack clarity and simplicity frequently delay ethics approval of research projects. The wording and content of the Information Sheet and Consent Form must be appropriate to the age and educational level of the research participants and clearly state in simple non-technical language what the participant is agreeing to. Use the active voice e.g. "we will book" rather than "bookings will be made". Refer to participants as "you" and yourself as "I" or "we". An appropriate translation of the Forms should be provided where the first language of the participants is not English. If you have different participant groups you should provide Information Sheets and Consent Forms as appropriate (e.g. one for children and one for parents/guardians) using the templates provided in Appendix I. Where children are of a reading age, a written Information Sheet should be provided. When participants cannot read or the use of forms would be inappropriate, a description of the verbal information to be provided should be given. Where possible please ensure that you trial the forms on an age-appropriate person before you submit your application.

SECTION D: APPROPRIATE SAFEGUARDS, DATA STORAGE AND SECURITY

D1

Will the research involve the collection and/or use of personal data?
☒ **Yes** ☐ **No**

Personal data *is data which relates to a living individual who can be identified from that data OR from the data and other information that is either currently held, or will be held by the data controller (the researcher).*

This includes:

- *any expression of opinion about the individual and any intentions of the data controller or any other person toward the individual.*
- *sensor, location or visual data which may reveal information that enables the identification of a face, address, etc (some postcodes cover only one property).*
- *combinations of data which may reveal identifiable data, such as names, email/postal addresses, date of birth, ethnicity, descriptions of health diagnosis or conditions, computer IP address (if relating to a device with a single user).*

If yes, is the research collecting or using special category data as defined by the GDPR 2018, for example data:

- which reveals racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership ;
- data concerning health (the physical or mental health of a person, including the provision of health care services) ;
- data concerning sex life or sexual orientation ; or
- genetic or biometric data processed to uniquely identify a natural person.

- **data which might be considered sensitive in some countries, cultures or contexts?**

Note that if you intend to process 'special category' information you will need an 'additional' legal basis for processing that particular data and further safeguards will need to be put in place.

<u>If yes</u>, state whether explicit ethical informed consent will be sought for its use and what data management measures are in place to adequately manage and protect the data.

A statement of good health i.e. denial of diagnosed medical conditions and lack of regular medication taking will be required for eligibility along with indication of known drug allergies but not formally recorded or verified. No additional details of health status will be taken.

D2

<u>During the Project</u> (including the write up and dissemination period)

State what types of data will be generated from this project (i.e. transcripts, videos, photos, audio tapes, field notes, etc).

Data will consist of 4 types: i) Personal (age, name, email address); ii) biological (derived from blood and blister fluid); iii) questionnaire/self-report on blister healing and iv) photos of the forearms

How will data be stored, including where and for how long? This includes all hard copy and electronic data on laptops, share drives, usb/mobile devices.

Electronic data will be stored on secure UCL servers, or where needed, password-protected, firevault encrypted personal laptops. <u>Paper records (e.g. Informed consent) will be digitised, stored on secure UCL servers and original paper copy will be securely destroyed by shredding.</u>~~Paper records (e.g. Informed consent) will be kept in locked filing cabinets on secure UCL premises~~. All data will be pseudo-anonymised via allocation of a study number and only linkable to an individual via a password protected master list kept on secure UCL servers. Only the PI and Applicant will have access to this document

After completion of the study the master sheet will be deleted to fully anonymise both the raw and analysed data. This will be stored indefinitely for future comparison and any necessitated retrospective analysis.

Biological samples will retained for a maximum of 5 years after completion of the study (est. 2028)

Who will have access to the data, including advisory groups and during transcription?

Only the study team - and if required - the Sponsor will have access to the data

D3

Will personal data be processed or be sent outside of the European Economic Area (EEA)*?

If yes, please confirm that there are adequate levels of protection in compliance with the General Data Protection Regulation 2018 and state what these arrangements are below.

No

D4

After the Project

What data will be stored and how will you keep it secure?

As above. All data will be fully anonymised after completion of the study and kept indefinitely. After transcription of the paper records to an electronic format they will be destroyed

Where will the data be stored and who will have access?

UCL servers with access only by the study team. There may be the need to share fully anonymised data with collaborators in the future

Will the data be securely deleted?

If yes, please state when will this occur:

Paper records at the end of the study, following transcription. Electronic records will not be deleted but instead fully anonymised

D5

Will the data be archived for use by other researchers? ☒ **Yes** ☐ **No**

If **Yes**, please describe provide further details including whether researchers outside the EEA will be given access.

Whilst this is not anticipated (this being a small, discrete study) we will store the anonymised data for future comparison, necessitated retrospective analysis or to enable collaborative research.

SECTION E: DETAILS OF RISKS AND BENEFITS TO THE RESEARCHER AND THE RESEARCHED

E1 **Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research participants).**

Risk assessments will be undertaken prior to commencement and any required mitigation activities completed. Cantharidin is not expected to pose significant occupational safety risk to site staff under proposed conditions of use and administration. Adequate precautions will be taken to avoid direct eye or skin contact and the generation of aerosols or mists. Venupuncture will be undertaken by appropriately trained individuals using ANTT. All vaccinations mandated by Occupational Health will be completed. All procedures and visits will take place at UCL in working hours.

E2 **Will these participants participate in any activities that may be potentially stressful or harmful in connection with this research?** ☒ **Yes** ☐ **No**

If **Yes**, please describe the nature of the risk or stress and how you will minimise and monitor it.

As discussed, the blistering process can be associated with minor, temporary skin discoloration. Whilst no scarring has previously been observed we will explicitly state in the PIS that this cannot be guaranteed. There is also a very small risk of infection. Venupuncture can cause mild discomfort. The Investigators are very experienced with all procedures associated with the proposed work and include a Clinician. Appropriate protective equipment, sterile dressings and technique will be employed throughout. All subjects will be followed up to ensure safe resolution and healing of the blister lesions. Cantharidin is potentially toxic but not at the dilutions, manner and quantity employed here. The anti-inflammatory drugs employed are commonly used for a multitude of conditions and are applied as a single dose, preventing long term effects and minimising exposure. As such we do not anticipate a significant risk of side effects.

E3 **Will group or individual interviews/questionnaires raise any topics or issues that might be sensitive, embarrassing or upsetting for participants?**

If **Yes,** please explain how you will deal with this.

No

E4 **Please describe any expected benefits to the participant.**

There are no direct benefits for the participants.

E5 **Specify whether the following procedures are involved:**

Any invasive procedure(s) ☒ **Yes** ☐ **No**

Physical contact ☒ **Yes** ☐ **No**

Any procedure(s) that may cause mental distress ☐ **Yes** ☒ **No**

Please state briefly any precautions being taken to protect the health and safety of the research participants.

There is a limited invasiveness and physical contact during the blister raising procedure. All procedures will be carried out on the forearm on UCL premises by experienced scientists. Phlebotomy will be carried out by qualified clinical staff.

E6

Does the research involve the use of drugs? ☒ **Yes** ☐ **No**

If **Yes**, please name the drug/product and its intended use in the research and then complete Appendix II

~~H~~Betamethasone 0.1% Cream~~ydrocortisone butyrate 0.1%~~. Used for the treatment of inflammatory skin disorders such as eczema, and contact dermatitis. This drug should elicit significant effects on the formation of the blisters and the migration of cells and fluid to the compartment whilst having no systemic effect. Used as a single dose/application no harm or side effects are anticipated

Prednisolone. Used for a variety of conditions as an oral anti-inflammatory agent. It is again anticipated to act as a 'positive control' suppressing the local inflammatory response induced by the blistering procedures. It will again be given as a single dose of 30mg to minimise exposure and the risk of side effects

Soft white paraffin is commonly employed as a moisturizer and is not thought to be 'active' pharmacologically

Does the project involve the use of genetically modified materials? ☐ **Yes** ☒ **No**

If **Yes**, has approval from the Genetic Modification Safety Committee been obtained for work? ☐ Yes ☐ No

If **Yes**, please quote the Genetic Modification Reference Number: N/A

E7

Will any non-ionising radiation be used on the research participant(s)? ☐ **Yes** ☒ **No**

If **Yes**, please complete Appendix III.

E8

Are you using a medical device in the UK that is CE-marked and is being used within its product indication? ☐ **Yes** ☒ **No**

If **Yes**, please complete Appendix IV.

CHECKLIST

Documents to be Attached to Application Form (if applicable)	Tick if attached
Section B: Details of the Project	
• Questionnaire(s) / Psychological Tests	☒
• Relevant correspondence relating to involvement of collaborating department/s and agreed participation in the research i.e. approval letters to gatekeepers seeking permission to do research on their premises/ in their company etc.	☐
Section C: Details of Participants	
• Parental/guardian consent form for research involving participants under 18	☐
• Participant/s information sheet	☒
• Participant/s consent form/s	☒
• Advertisement	☒
Appendix I: Information Sheet(s) and Consent Form(s)	☒

Appendix II: Research Involving the Use of Drugs

- Relevant correspondence relating to agreed arrangements for dispensing with the pharmacy ☐
- Written confirmation from the manufacturer that the drug/substance has has been manufactured to GMP ☐
- Proposed volunteer contract ☐
- Full declaration of financial or direct interest ☐
- Copies of certificates: CTA etc… ☐

Appendix III: Use of Non-Ionising Radiation ☐

Appendix IV: Use of Medical Devices ☐

Updated October 2019